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Interventions for (Ultra-)Rare Disorders and the Logic of Cost Effectiveness

The Need for Alternative Methods to Evaluate Medical Interventions for Ultra-Rare Disorders

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INNOVAL HC
Institute for Innovation & Valuation in Health Care

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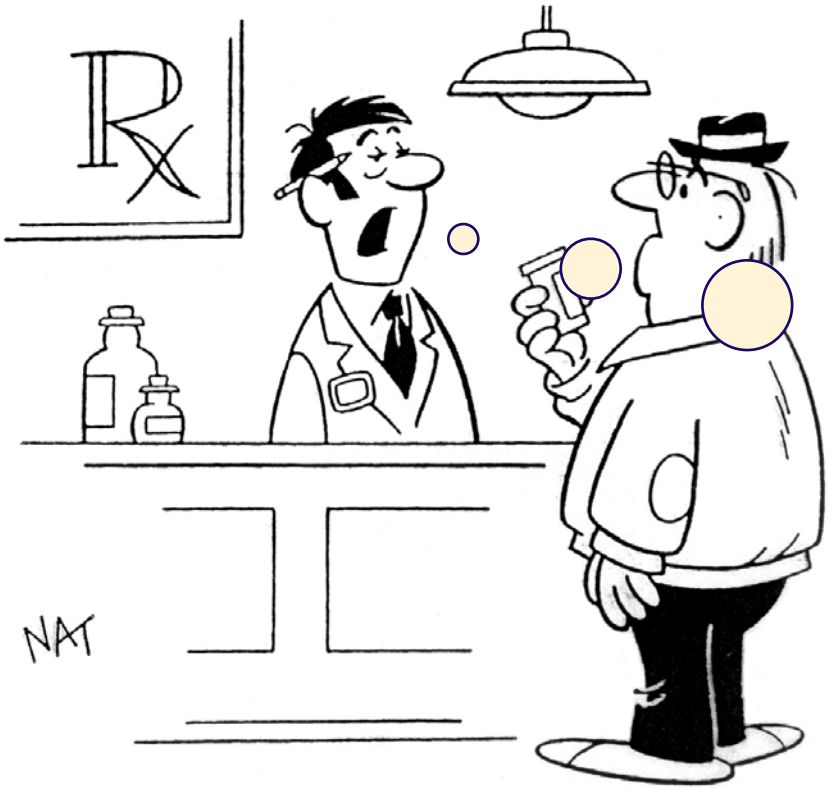


"The drug itself has no side effects – but the number of health economists needed to prove its value may cause dizziness and nausea."

INNOVAL HC
Institute for Innovation & Valuation in Health Care

Who We Are

- Independent Not-for-Profit Organization
  - Not a Commercial Contract Research Organization
- Founded in Aschaffenburg/Germany in June 2005
  - Offices in Wiesbaden/Germany since December 2008
- Member of the Stockholm Network
  - Group of European Market-Oriented Think Tanks
- Formally associated with University of Ludwigshafen
- Funding of Projects
  - Under an "unrestricted educational grant" policy
  - Supported by National Institute of Mental Health (NIMH), Bethesda, MD; Official HTA Agencies; DFG; DKFZ; Physician and Payer Organizations; Industry (>80% international projects – AUS, CAN, UK, USA, …)
- Prof. Michael Schlander, MD, PhD, MBA (Heidelberg & Ludwigshafen)
- Prof. Oliver Schwarz, PhD (Heilbronn)
- Prof. Erik Trott, MD, PhD (Würzburg & Aschaffenburg)

International Orphan Drug Legislation

- USA: Orphan Drug Act (1983); Orphan Drug Regulation (1993)
- Japan: Orphan Drug Regulation (1993)
- Australia: Orphan Drug Policy (1997)
- European Union: Regulation CE No. 141/2000 (2000)

Some Measures:

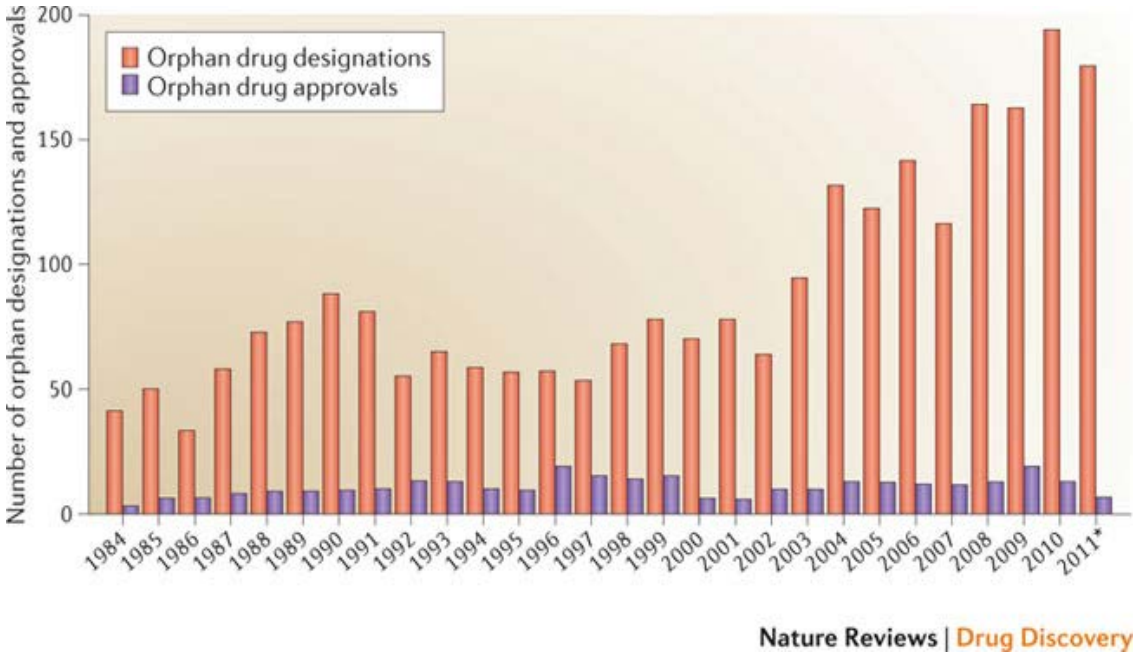
- R&D grants, tax credits, protocol assistance, accelerated review, market exclusivity (USA, 7y; Japan and EU, 10y; Australia, 5y)

Some Definitions:

- USA: prevalence < 7.5/10,000 (i.e., <200,000)
- Japan: prevalence <4/10,000
- Australia: prevalence <1.1/10,000
- European Union: prevalence <5/10,000
- EU Clinical Trials Directive 2014, England / Wales: “ultra-rare” disorders, prevalence <1/50,000

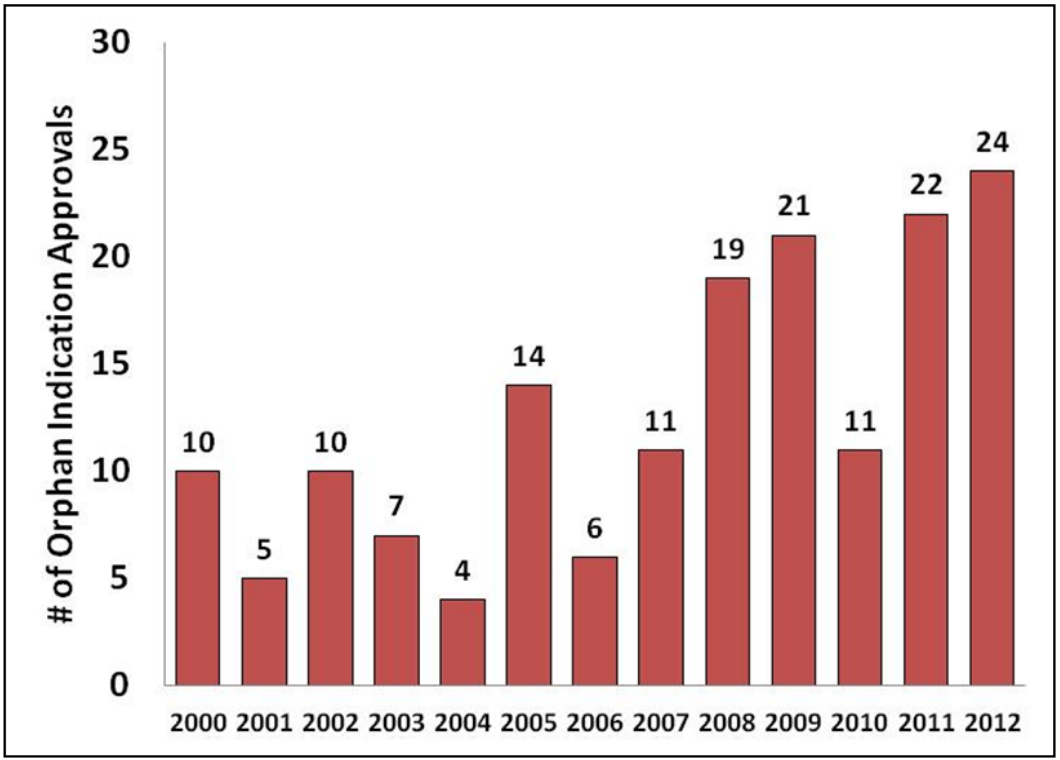
Impact of Orphan Drug Legislation

Orphan Drug Designations and Approvals, U.S.A., 1984-2011



Source: I. Melnikova: Rare Diseases and Orphan Drugs.
Nature Reviews Drug Discovery 2012, 11 (4): 267-268, Fig. 1 (© Macmillan Publishers Ltd.)

Impact of Orphan Drug Legislation

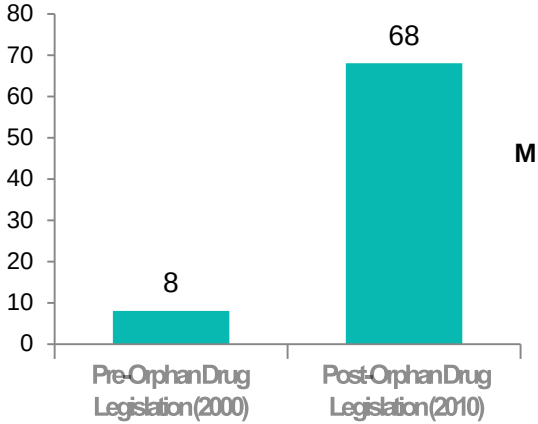


Source: http://www.biotech-now.org/wp-content/uploads/2013/03/Historic-Orphan-Drug-Approvals.png

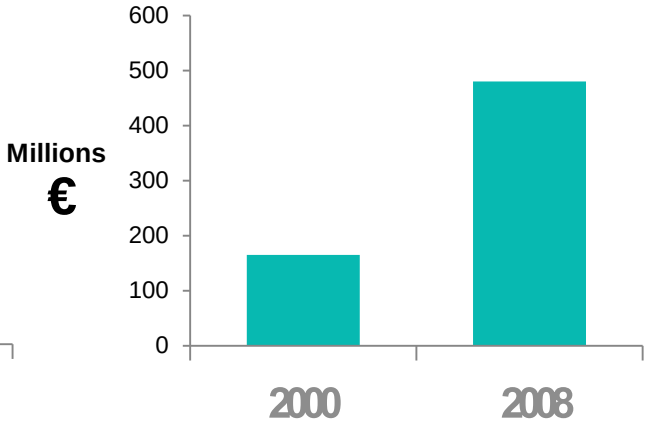
EU Orphan Drug Regulation

Impact on Research & Development

No. of Drugs for rare diseases receiving marketing authorization in Europe

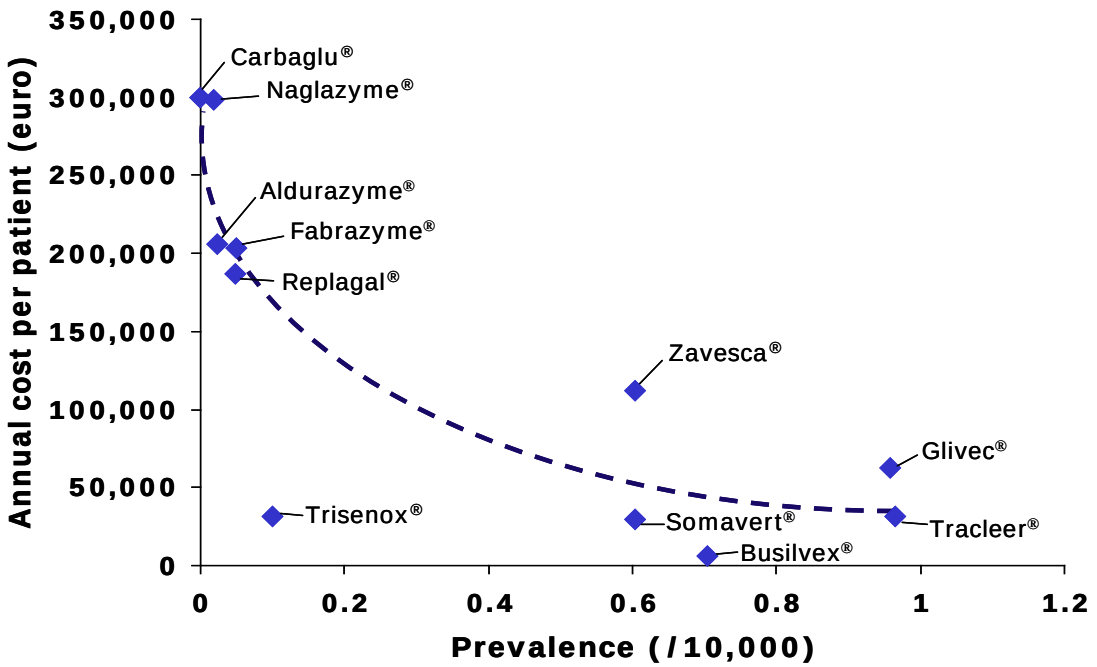


European investment in orphan drug R&D, 2000 and 2008



Source: Office of Health Economics (OHE).
Assessment of the Impact of OMPs on the European Economy and Society. Consulting Report November 2010.
Available at http://www.ohe.org/publications/article/assessment-of-the-impact-of-orphan-medicinal-products-on-europe-15.cfm . Last accessed 14/01/12.

Higher Cost per Patient Related to Rarity



Limited Budget Impact of Orphan Drugs

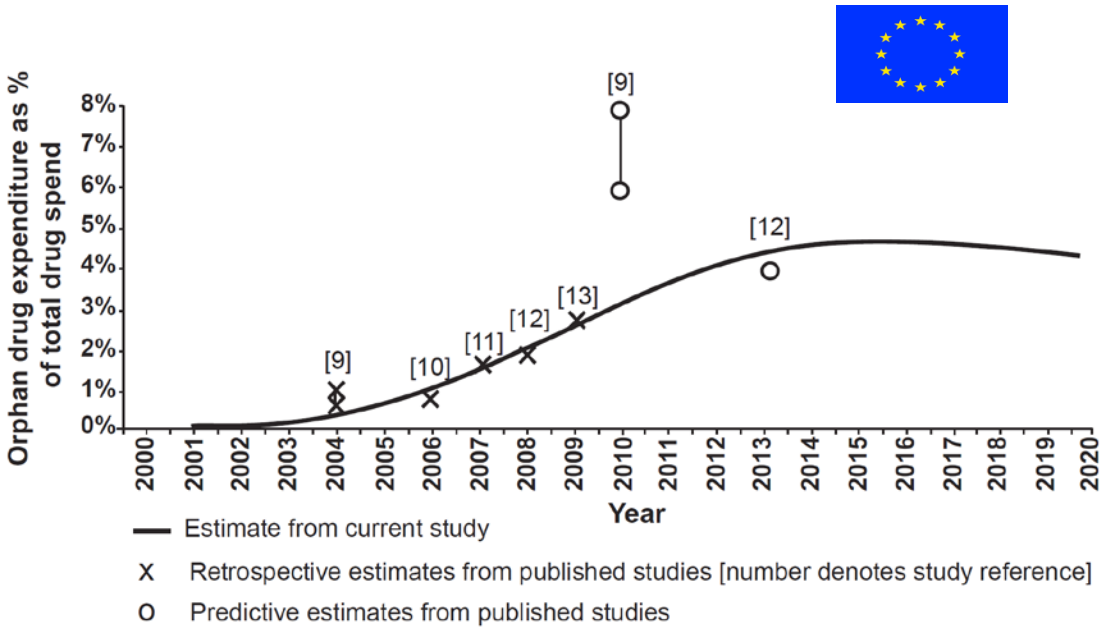
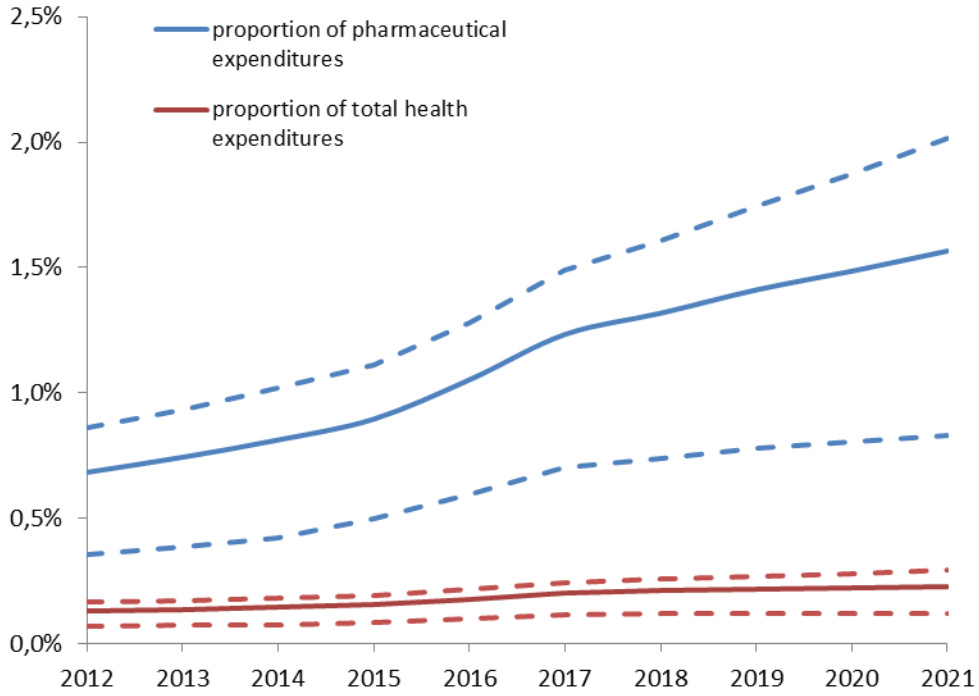


Figure 3 Budget impact of orphan drugs as percentage of total pharmaceutical spend (2002 - 2020).

Schey et al. Orphanet Journal of Rare Diseases 2011, 6:62 http://www.ojrd.com/content/6/1/62

Source: Orofino et al. (2010)

Expenditure on Ultra-Rare Disorders



Schlander et al. (2014) in press

Countries have different funding policies specific to rare and ultra-rare diseases

Country	Body	Specific approaches
England, Scotland, Wales	NICE, SMC, AWMSG, NHS England	Specific approach to ultra-rare diseases with NICE's Highly Specialised Technology appraisal, SMC ultra-rare and AWMSG ultra-orphan approaches. SMC has another alternative approach to rare and end-of-life drugs.
Germany	GBA/IQWIG	Orphan drugs with a projected budget impact of <€50M per year are not required to submit cost analysis and added value is assumed in line with the EMA COMP.
Netherlands	Zorg Institute	In-patient orphan funding is conditional approval based on a 4 year reassessment of real world data, requires cost effectiveness but no threshold.
Norway, Ireland, France, Poland, Portugal, Sweden	NOMA, NCPE, HAS, AOTM, INFARMED, TLV	Apply classical approaches of cost effectiveness to orphan drugs, in France for budget impact in Yr. 2>€20million. All are researching alternative approaches for assessment of rare and ultra-rare diseases.

How to Evaluate Interventions for URDs?

- **Two International Expert Workshops**
  - in conjunction with Annual European ISPOR Congresses in Berlin / Germany, November 08, 2012, and in Dublin / Ireland, November 07, 2013
  - supported by BioMarin and Genzyme under an unrestricted educational grant policy
- **Objective to Seek Agreement**
  - on challenges that arise when applying conventional HTA methodologies to ultra-rare disorders (URDs)
  - on the need for (improved or) alternative evaluation methods, ideally in the form of a Consensus Statement
  - on promising ways forward, overcoming the shortcomings of currently prevailing evaluation paradigms

[1]Alexion (2012) and Genzyme (2013), respectively

How to Evaluate Interventions for URDs?

- **Two International Expert Workshops**[1]
  - Silvio Garattini (Mario Negri Institute, Milan / Italy)
  - Sören Holm (U of Manchester / England)
  - Peter Kolominsky (U of Erlangen / Germany)
  - Erik Nord (U of Oslo / Norway)
  - Ulf Persson (IHE, Lund / Sweden)
  - Maarten Postma (U of Groningen / The Netherlands)
  - Jeffrey Richardson (Monash U, Melbourne / Victoria)
  - Michael Schlander (U of Heidelberg / Germany)
  - Steven Simoens (U of Leuven / Belgium)
  - Oriol de Sola-Morales (IISPV, Barcelona / Spain)
  - Keith Tolley (Tolley HE, Buxton / England)
  - Mondher Toumi (U of Lyon / France)

[1]supported by BioMarin (2012 and 2013) and by Alexion (2012) and Genzyme (2013), respectively

How to Evaluate Interventions for URDs?

- **Approach Chosen (Method)**
  - open exchange of views under the Chatham House Rule
  - subsequent to the workshop,
    iterative process leading to final consensus document
- **Subject of Analysis**
  - technologies targeting ultra-rare disorders (URDs), excluding cancer and personalized medicine
  - URDs under consideration should be
    - severe,
    - chronic,
    - represent clearly defined biological entities (i.e., are not created by artificial “slicing” of a biologically much broader and more prevalent indication),
    - are associated with a broadly accepted high unmet medical need

How to Evaluate Interventions for URDs?

- **Situation Analysis**
  - The workshop participants agreed to begin with a review of the current situation and challenges.
  - The group agreed to focus on a high-level analysis (1, below):
- **Levels of Analysis**
  1. **principles underlying the current evaluation framework**
  2. actual evaluation policies implemented by HTA agencies and regulatory bodies (primarily those concerned with pricing and reimbursement decisions)
  3. evaluation practice when principles and policies are applied to real-world problems.

     In particular, the third level of analysis would have to include case studies, including cases where existing regulation has been potentially misused.

Key Challenges for URDs

- **Establishing Evidence of Clinical Effectiveness**
  - usually very small number only of physicians with specialized expertise, who tend to be based in few specialized centers;
  - often limited clinical understanding of disorder;
  - often limited understanding of natural history of disorder;
  - often limited availability of validated instruments to diagnose and measure disease severity / progression;
  - often resulting in difficulties to generate a large volume of clinical evidence based on RCTs, which may lead to
  - higher levels of uncertainty surrounding effect size estimators;
  - small numbers of patients are often geographically dispersed, resulting in the need to establish multiple clinical trial sites for only a small number of patients;
  - …

Key Challenges for URDs

- **Establishing "Value for Money" (Efficiency)**
  - international heterogeneity in institutional arrangements and established methodologies to determine "value for money";
  - the still prevailing "logic of cost-effectiveness", relying on cost per QALY benchmarks, in applied health economics;
  - the broadly held assumption that the social desirability of an intervention would be inversely related to its associated incremental cost per QALY gained;
  - the adoption of "efficiency-first" instead of "fairness-first" evaluation approaches in a number of jurisdictions;
  - the high fixed (i.e., volume-independent) cost of R&D and the need to recoup this investment from a small number of patients during limited periods of market exclusivity;
  - …

Three Areas of Concern

Normative Reasons for Concern

- (Quasi) Utilitarian "efficiency-first" framework, implying
- distinct difficulties to incorporate rights-based reasoning.

Empirical Reasons for Concern

- Studies overwhelmingly indicate that the majority of people do not wish QALY maximization, and suggest
- a wide range of social preferences (other than QALY maximization).

Methodological Reasons for Concern[1]

- Valuation results (for VSL / QALYs, and for health state utilities alike) differ greatly as a function of the methodology chosen.

[1]not addressed here

What are the Objectives of Health Care?[1]

Utilitarian Thought[2]	Deontological Thought[2]
Economic Welfare Theory (ordinal utilitarianism) **Extrawelfarism** (cardinal medical utilitarianism)	**Health Care Sector** (Majority of) Professionals and the Public
	Stated (Official) Objectives Policy Makers, Payers, Providers
	Historic Roots of Medicine and Health Care
	"Empirical Ethics" (Public Preferences)
	Legal Environment (Constitutional Provisions)
Moral Intuitions (e.g., Bentham, Mill, Harsanyi)	**Moral Intuitions** (e.g., Kant; Rawls, Daniels; Sen)

[1]Related to collectively organized systems of health care delivery and financing, [2]and a dilemma, resulting from the absence of the one compelling, integrating "grand theory"? – cf. Thomas Nagel: *The Fragmentation of Value* (1979) ; source of rhis chart: M. Schlander (2005): *Economic evaluation of medical interventions: answering questions people are unwilling to ask?* Paper presented to the International Health Eco nomics Association (iHEA) 5th World Congress, Barcelona, Spain, July 9-15, 2005.

Vertical versus Horizontal Equity

Rights as Goals:

- "To fail to satisfy people's basic needs and provide essential skills and opportunities is to leave people without recourse, and people without recourse are not free."
  (A. Sen, 1984; C. Korsgaard, 1993)
- Vertical equity as "positive discrimination" (cf. G. Mooney, 2000)

Relevant Legal Provisions:

- Human Rights Legislation
- Constitutional Provisions (…)
- Nondiscrimination and Rights of Persons with Disabilities
- EU Disability Legislation
- UK Equality Act
- …

Empirical Ethics

The "Sharing Perspective":

A Broad Range of Social Preferences

- severity of the initial health state,
  i.e., a stable preference to prioritize health care for the worse off;
- urgency of the initial health problem,
  especially if life-threatening, i.e., the so called "rule of rescue";
- capacity to benefit of relatively lower importance,
  i.e., people appear to value additional health gains lower once a certain minimum effect has been achieved;
- certain patient attributes (such as [younger] age, parent or caregiver status, [non] smoker);
- a strong dislike for "all-or-nothing" resource allocation decisions;
- rights-based considerations (such as nondiscrimination).

Potential Ways Forward

Evidence of Clinical Effectiveness:

- Approval based on surrogate endpoints should be accepted as an interim solution only.
- Conditional reimbursement to ensure rapid patient access may be linked to "coverage with evidence development" agreements.
- Even at prevalence rates as low as 1/50,000 (the URD qualifier), there would be about 10,000 patients in Europe.
- Thus it should be possible to set up multinational RCTs designed to show relevant clinical endpoint benefit.
- If necessary, such trials might be supported by the not-for-profit *European Clinical Research Infrastructure Network* (ECRIN).

Potential Ways Forward

Perspectives on Cost:

- From a decision-makers' perspective, overall budgetary impact should be more relevant than incremental cost effectiveness ratios.
- If a social value perspective (instead of an almost exclusive focus on individual utility) was adopted, the social opportunity cost (or [social] value foregone) of adopting a program would be reflected by its net budgetary impact. This would move the focus from cost per patient to cost on the program level.
- Likewise, a pragmatic approach would reflect the commercial realities and the basic cost structure of the research-based biopharmaceutical industry, which incidentally is showing signs of a strategic shift from price maximization to life cycle revenue management (in order to "extract" maximum value).

Potential Ways Forward

Valuation Principles:

- **Alternative** economic (e)valuation principles – that promise to reflect normative concerns and capture social preferences better than the conventional logic of cost effectiveness – should be rigorously assessed for their potential to complement of replace the currently predominant standard.
- **Candidates** include (but are not limited to)
  - cost value analysis, using the person-trade off or the relative social willingness-to-pay method;
  - a multicriteria decision analysis framework, which, in principle, might incorporate cost utility analysis with benchmarks adjusted to multiple contextual variables;
  - the use of alternative methods to value benefit.

Thank You for Your Attention!

Professor Michael Schlander, M.D., Ph.D., M.B.A.

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The URD Consensus Document will be made available for download at the Institute's website, **www.innoval-hc.com**